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Electrophysiological profiling of escitalopram in rodents and human healthy subjects

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INTRODUCTION

Major depressive disorder (MDD) is a severe and common psychiatric disorder and although it primarily involves mood disturbances, patients usually present alterations in cognitive function. Cognitive performance is assessed through the use of behavioural tasks but this does not allow for the establishment of a pharmacodynamic marker of underlying brain activity. Identifying neurophysiological markers with a correlation to cognitive performance could increase the clinical utility of pharmacological compounds. This study was aimed at exploring neurophysiological pharmacodynamic markers of cognitive performance for escitalopram, a selective serotonin reuptake inhibitor (SSRI). SSRIs have been the leading class of drugs for the treatment of depression and anxiety for several decades and have been associated with a number of sensitive peripheral and central biomarkers. Quantitative electroencephalography (qEEG) and auditory steady-state responses (ASSRs; electrophysiological responses entrained to the frequency and phase of a rapid auditory stimuli) were investigated in human healthy subjects and Wistar rats following treatment with escitalopram.

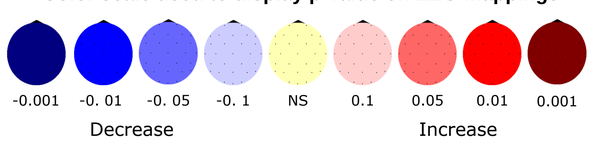
Human

METHODS

Thirty two healthy male subjects, 18-45 years old, participated in a four-way double-blind cross over study during which they received placebo, escitalopram (15 mg) or two dose levels of a test drug (not reported here) for three days and in a randomized order. Each treatment was administered orally and separated by at least 18 days' wash-out period. Using 28 leads with 2 bipolar leads for artifact removal and a sampling rate of 400Hz, resting and vigilance-controlled EEG was recorded and complete event-related potential (ERP) was tested on the day preceding the first dose (baseline) and on days 1 and 3 of dosing.

The following statistical analysis sets were used: *all-subjects-treated set* (ASTS) – all randomised subjects who took at least 1 dose of investigational medicinal product (IMP); *pharmacodynamics-analysis set* (PDS) – all subjects in the ASTS with at least 1 assessment of the relevant pharmacodynamic parameter for at least 1 dose of IMP. For each of the EEG endpoints, a mixed model for repeated measurements was performed. To avoid cross-level bias when using with-in period baseline measurements as covariates, the baseline measurements were modelled with the outcome variable for Day 3, in compliance with the principles described by Kenward and Rogers. The treatment-specific least squares (LS) means and the pair-wise treatment contrasts were estimated with 95% confidence intervals (CIs) and p-values for no difference.

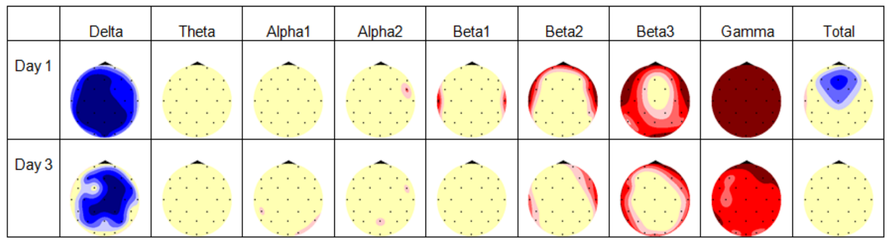
Color scale used to display p-value on EEG mappings



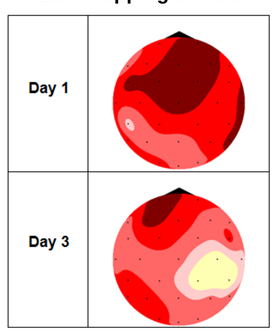
RESULTS

- Increase in power of fast waves (β and γ) in both resting and vigilance-controlled conditions. The spread was on most of the 28 electrodes flat maps and effect was more pronounced on day 1 than 3.
- Decrease in power of slow wave (δ) in resting conditions (day 3) and vigilance-controlled conditions (days 1 and 3).
- P300 (amplitude or latency) unaffected
- ASSR increased on Days 1 and 3.
- No consistent pattern in pair-wise comparisons of auditory evoked gamma power or on the ERN (error-related negativity obtained on false alarm of Flanker task) or LMT (learning memory task) late potential wave amplitude.
- Slight increase in the error positivity (Pe) potential following ERN.

Statistical assessments on qEEG in Resting condition on Absolute powers



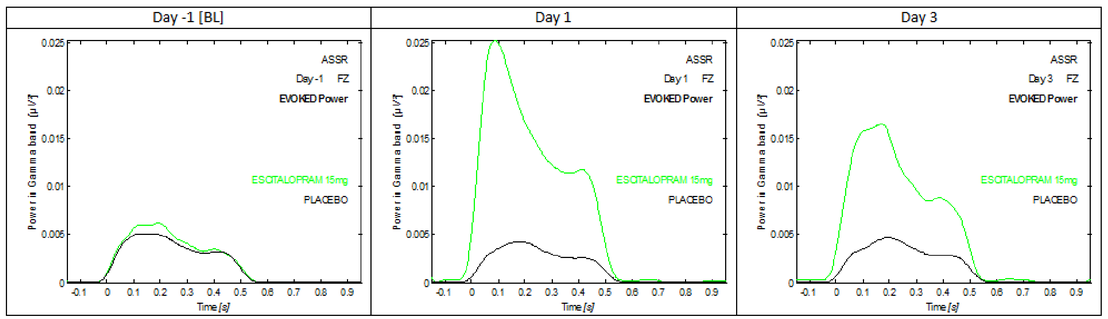
EEG mapping of ASSR



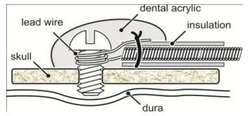
Statistical comparisons of treatments versus placebo for each visit corrected by Day -1 values

Human ASSR – Powers in Gamma Band

Statistical comparisons of treatment versus placebo for each visit corrected by Day -1 values



Rat

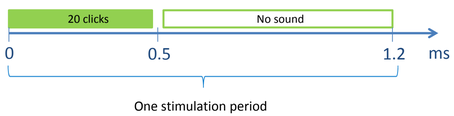


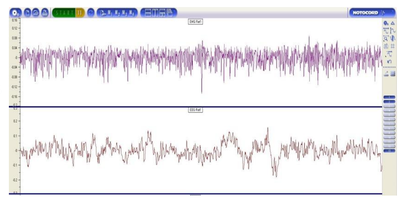
- DSI Telemetry System
- Transmitter device positioned subcutaneously
- Recording is over large area of the brain including both hemispheres
- EMG recording was used to remove movement artifacts

Rats are freely moving

High quality EEG & EMG signals

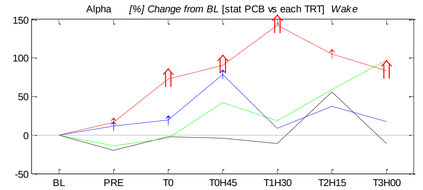
ASSR protocol





EFFECTS OF ESCITALOPRAM ON POWER SPECTRUM or ASSR

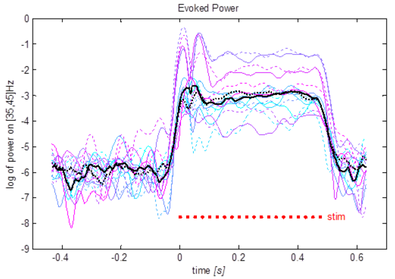
qEEG



Vehicle, 2 mg/kg, 10 mg/kg, 20 mg/kg

Escitalopram treatment caused a dose-dependent increase in power in the α band on wake EEG, with the effect of the 20 mg/kg dose lasting >3 hours. Similar results can be observed in the β1 band.
Results are less pronounced in other bands and other rodent sleep states (SWS and REM).

ASSR



Vehicle, Treatment, Mean

Each color represents the results of one rat. The graph shows the evolution of the evoked power before and during the auditory stimulation. Escitalopram at 10 mg/kg does not significantly modify ASSR.

CONCLUSIONS

In heathy human subjects, escitalopram induced a marked increase in power of the fast waves (β and γ) in both resting and vigilance-controlled conditions and a decrease in power of the slow wave (δ). In addition to the spectral power, other paradigms focusing on cognitive processes such as the oddball paradigm were used. Late evoked potentials P300 were not affected by escitalopram while spectral analysis of the P300 wave revealed an increase in the gamma band that may be not task specific but rather correspond to the overall effect on gamma power. Unlike evoked gamma (ASSR) which Is more localized on frontal or fronto-central electrodes, the increase in power in the resting state was homogeneously spread on the scalp. The gamma band is a domain of growing interest as a potential biomarker in psychiatric disease and it is considered to reflect synchronization mechanisms between distant neuronal populations, playing a role in all sensory and cognitive tasks. The profile was somewhat different in the rat, with increases in the α and β1 bands and no effect on ASSR. One potential explanation for the species differences may be that escitalopram did not have identical pharmacological actions in human and rat, particularly since the doses used were relatively high. Activity of escitalopram at potassium ion channels (e.g. TREK-1; Lin et al., 2015) and sigma-1 receptor chaperones (Ishima et al., 2014) has recently been described, which may further explain species-specific effects.

Lin et al. CNS Neurosci. Ther. 2015 Jun;21(6):504-12
Ishima et al. Eur. J. Pharmacol. 2014 Mar 15;727:167-73

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